REMARKS

A Notice of Non-Compliant Amendment was mailed March 12, 2010 which stated that the amended paragraph did not include markings. The paragraph in question, at page 2 of the Amendment of March 5, 2010, is an inserted paragraph which under 37 CFR§1.121(b)1)(iii) is not to be underlined. For this reason, it is requested that this objection be withdrawn. Minor amendments to the status identifier of claim 1 and the text of claim 58 have also been made. Claims 1, 4-7, 11-15, 18-27, 32-33, 36-39, 43, 45-47 and 50-72 were rejected under 35 U.S.C.§112, second paragraph for failing to particularly point out and distinctly claim the subject mater that the applicant regards as the invention.

Reconsideration is requested.

The Examiner stated that the term "ratio" as used in the claims 1, 11, 18-19, 33, 43 and 50-51 was unclear. In response, the claims have been amended to insert the word "weight" before the word "ratio". The basis for this is the description in the specification in paragraphs 0016 and 0017 and in original claim 19. This amendment adopts the Examiner's suggestion and it is requested that this ground of rejection be withdrawn. Claim 7 has been amended to delete the trademark and the reference to the USP in favor of the adoption of the chemical name for the commercial products. Under the provisions of MPEP 608.01(v), the applicant may amend a patent application to insert the identification of a trademarked product provided a showing is made that the nature of the product was known at the time that the patent application was filed.

Attached are the cover sheets, with a copyright date of 2000, and pages 401-405 of The Handbook of Pharmaceutical

Excipients, Third Edition, A.H. Kibbe, Editor, which identifies the chemical composition of Eudragit RSPO; Eudragit RL and Eudragit NE 30D. The chemical definition of the Eudragit products has been inserted into amended claim 7 and into the specification at page 20, line 12. For these reasons, it is requested that this ground of rejection be withdrawn.

Claims 1, 4-7, 11-15, 18-27, 32-33, 36-39, 43, 45-47 and 50-72 were rejected under 35 U.S.C. §103(a) as being unpatentable over Timmins et al.(Timmins) in view of Boswell.

Reconsideration is requested.

Claims 4, 5, 21, 22, 24, 25, 33, 36,-39, 43, 45, 50, 51, 53, 54, 56 and 59 have been canceled. Claim 1 has been amended to include the substance of canceled claims 54 and 56 and the remaining claims have been made directly or indirectly dependent on amended claim 1 Claims 54 and 56 pointed out specific antidiabetic drugs that are now recited in amended claim 1.

Modified pharmaceutical dosage forms that utilize a matrix dosage form for the controlled release of highly soluble drugs, often do not provide adequate control over the release rate and result in a drug release profile that approximates first-order kinetics and often results in dose dumping or a burst release that makes the matrix formulation unacceptable for use with soluble drugs. However, since many modified release dosage forms contain comparatively large amounts of highly soluble active ingredient it is often necessary to include large amounts of suitable excipients to achieve appropriate controlled release profiles. This results in an over sized dosage form which causes patient rejection due to the difficulty in swallowing the over sized dosage form. This is acknowledged by Timmins (col.4, lines 58-61) Hence a technique is needed, which can effectively control the release of the highly soluble active ingredient without requiring an over sized dosage form.

The Timmins patent discloses a biphasic controlled release delivery system for highly soluble drugs such as metformin hydrochloride, which has prolonged gastric residence and the property of swelling following contact with gastric fluids. The major limitation of the Timmins dosage formulation is that it provides a very bulky formulation for higher doses of the metformin hydrochloride that is very inconvenient for human consumption. For instance, the cited example provides a formulation of 500mg metformin with a tablet weight of 1.0gm.

It is apparent from the Timmins specification that the Timmins dosage formulation operates by increasing the time that the dosage remains in the stomach because the dosage formulation is designed to swell in the stomach so that the dosage formulation will have a prolonged residence time. This essential functional characteristic can only be achieved by the use of polymers that swell on contact with water. (Cf. Timmins col.20, lines 55-60). Therefore, although Timmins has disclosed a dosage formulation having an inner solid particulate phase and an outer solid continuous phase that uses one or more hydrophilic polymers, one or more hydrophobic polymer and/or one or more hydrophobic materials, the Timmins composition must contain at least one hydrophilic polymer, as shown by reference to all of the enabling examples of that patent. Amended claim 1 points out that the micro matrix particles consist of an active drug and a hydrophobic agent. This language excludes the hydrophilic agent.

Hence, in the implementation of the teachings of Timmins, a skilled person in the art would be directed to use at least one hydrophilic polymer in following the teachings of Timmins as to the making a sustained release formulation. The claims of the present application point out a formulation which contains hydrophobic polymers which are not made obvious by the hydrophobic polymers recited in claim 1 of the present application

and the claims that are dependent on claim 1. New claim 73 points out that the dosage form consists of the recited ingredients which do not include a hydrophilic component as required by Timmins. Hence, Timmins does not make the instant invention obvious. Claim 1 specifically recites micromatrix particles that use only hydrophobic polymers to prepare the sustained release component.

Furthermore, it is not disputed that matrix formulations of highly soluble drugs will require high amounts of polymers to achieve a controlled release profile. This results in an increase in the size of the dosage form and has been acknowledged by Timmins. The knowledge of the increased size does not suggest the dual retard technique as pointed out in the claims of the present application. Thus, Timmins does not teach how one can reduce the overall size of dosage form while incorporating high amounts of drug in the composition.

In Timmins, the final size of the dosage form becomes very large due to large quantity of hydrophilic polymer required and thus the Timmins approach to formulations of drugs that must be administered in high doses (1000mg), such as metformin, is not practical due the difficulty the patient will have in swallowing a very large size dosage form. This problem is exacerbated in older patient populations who often take these medications. If a dosage form containing a single drug becomes very large in size because of the addition of another agent to the dosage form, the teachings of Timmins will not solve the problem.

The instant invention, as pointed out in claim 1, is directed to a combination containing a high dose of a highly soluble drug in a sustained release form and a low dose drug in immediate release form. Thus, if Timmins approach of formulation is adopted the final dosage form will become very large and unpalatable.

The following Table is derived from Timmins and it illustrates the high amounts of polymer relative to the active pharmaceutical ingredient (API) that result from the Timmins technique.

Example-1	500g API + 376.5g polymer	75% polymers by wt of API
Example-2	500g API + 391g polymer	78% polymers by wt of API
Example-3	500g API + 408 g polymer	81% polymers by wt of API
Example-4	500g API + >400 g polymer	81% polymers by wt of API

If we compare examples for the preparation of micromatrix particles of the same drug as shown in the present specification (e.g. Example 6 & 9 having about 26-28% polymer), the final size of the dosage form will actually be much smaller as compared to the Timmins dosage form. This will make it possible to combine a high dose, high solubility drug in sustained release form with low dose active in IR form and at the same time to restrict the size of the dosage form. This is clear from all the examples of the Timmins, which only contains 500mg of drugs, whereas with instant invention it has become possible to prepare dosage form of 1000mg of active that too in combination with other drug, while keeping the size of final dosage form suitable for swallowing.

Thus, it is clear from above that the problem, if the teachings of Timmins are applied, any person skilled in art would end up having large sized dosage form for highly soluble drugs.

As mentioned above another common problem with modified release dosage form of highly soluble drugs is dose dumping or a burst effect in-vivo.

In the present specification at paragraph [0098], it was disclosed that: "FIGS. 6 and 7 show release of high dose, high solubility active agent 11 & 12 and 15 & 16 as per example 1 & 2 respectively from a dosage form prepared using dual retard technique as described in the present invention and the release of high dose, high solubility active agent 13 & 14 and 17 & 18 as per example 3 & 4 respectively from a dosage form prepared without using a dual retard release technique. The total quantity of the hydrophobic release controlling agent is the same in all of the dosage forms in spite of the fact that the figures clearly show that dual retard technology significantly reduces the burst effect and effectively controls the release rate of the high dose, high solubility active ingredient for prolonged period. Paragraph [0162] also discloses the same conclusion.

The quoted section of the specification indicates that to achieve a desired release profile without having a burst effect, it is necessary to use a reduced amount of polymers in the dual retard technique as it is employed in instant invention for the preparation of micromatrix particles, as recited in the claims of the present application.

Timmins teaches a drug delivery system which achieves extended gastric residence by virtue of size but does degrade in vivo so as not to cause obstruction of the gastrointestinal tract. Thus, Timmins is strictly limited to gastroretentive dosage forms and teaches away from any other type of dosage form that does not swell in the stomach in order to retard its passage in the gastrointestinal tract.

Timmins does not teach such a specific combination of agents having different solubility. In addition, Timmins does not

disclose or suggest a dosage form where the top surface is not covered by the outer portion as pointed out in claim

Boswell discloses medicinal tablets, and in particular, a tablet of the type containing substantially segregated quantities of the same or different ingredients. Boswell discloses a tablet having two different ingredients particularly when they are incompatible and which needs to be protected or separated from one another.

Boswell also discloses that either the inlay portion or the main body portion must be formed from a coated granulation to resist assimilation in the gastrointestinal fluids (col. 3 lines 30-35) by having an enteric coated component. It further describes a tablet having a main body portion and two separate inlay portions at opposite sides of the tablet. However, it does not teach the dosage form which comprises a combination of high dose high solubility drugs in sustained release form and low dose active in immediate release form. Even all the enabling examples use enteric coatings. In applying the teachings of Boswell, any skilled person would be motivated to formulate the inlay tablet having at least an enteric coated component in order to resist assimilation of one of the active ingredient in the gastrointestinal fluids. Moreover, it also does not teach the compact sustained release dosage form of high dose highly soluble drugs in combination with low dose active.

None of the prior art teaches such a technique for high dose high solubility drugs, which reduces burst effect and also reduces the size of the dosage form.

The following chart compares a dosage from made by the assignee of the Timmins patent and a dosage form according to the present invention,. This comparison shows the reduction in size that is possible by the present invention.

Comparison of Commercial Tablet (US appl. No. 10/630,446 vs. BMS-Assignee of cited prior art i.e. Timmins)

Product detail	Product content	Shape	Weight of the product	Dimensions(length x width x thickness)
Glucophage XR as per prior art ; Timmins	Metformin sustained release (500mg)	Capsule shaped	1020.0mg	19.11mm x 9.4mmx 6.7 mm
Product of US application no: 10/630,446 (Enselin2 MF)	Rosiglitazone 2mg+ Metformin Sustained Release 500mg Tablet	Capsule shaped	784.0mg containing inner/outer portion weighing 90.0mg/694.0mgrespectively	14.95mm X 8.35mm x 6.3mm

Claim 1 also points out that the inner portion is covered by the outer portion from all the sides except a top surface that remains uncovered. This feature is not made obvious by Timmins and it would not be obvious to provide such a feature in the Timmins product which contains a hydrophilic component. The exposure of the hydrophilic component of Timmins, in a tablet having an uncovered top surface, would tend to distort the release profile taught by Timmins and one skilled in the art would not be directed to provide such a feature based on Timmins. Boswell when combined with Timmins does not suggest the uncovered top as one would not tamper with the release system taught by Timmins because of the reasonable expectation that the release properties would be affected to the point that dose dumping would be expected.

For these reasons, Timmins alone or in combination with Boswell does not teach the claimed dosage form of the claims which is a combination of ***a high dose, high solubility active ingredient***, as a modified release and low dose active ingredient as immediate release, which uses a reduced quantity of polymers to

control the release of a high dose, high soluble drug while providing a compact dosage form suitable for swallowing.

For these reasons, it is requested that this ground of rejection be withdrawn.

An early and favorable action is earnestly solicited.

Respectfully submitted,

James V. Costigan
Registration No. 25,669

Hedman & Costigan, P.C.,
1185 Avenue of the Americas
New York, NY 10036
(212) 302-8989